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REVIEW

Prostaglandin E and F receptors in the uterus

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Prostaglandins (PGs) are necessary for normal female reproduction. PGs act via their respective receptors and execute various functions in their target tissues depending on which type of receptor being activated. PG receptors are G-protein coupled receptors mediating various vital processes in the uterus throughout the reproductive cycle and pregnancy. They are essential for the normal functioning of uterine endometrium, myometrium and cervix. In this mini review, we explore the expression, functions and regulations of EP1-4 and FP in uterus. Recent reports show that PG receptors are regulated spatio-temporally in endometrium throughout the reproductive cycle. In myometrium, EPs and FP are differentially expressed and have prominent roles in the contraction and relaxation of the smooth muscle. In the cervix, PG receptors are essential for normal cervical ripening. PG receptors are important in several reproductive functions including reproductive cyclicity, embryo implantation, embryo spacing, uterine contraction or relaxation, and cervical ripening. Flawed regulation or signaling by PG receptors lead to many pathological conditions of the female reproductive tract such as dysmenorrhea, menorrhagia, endometriosis, cancer and pre-term or post-term pregnancies. Although several studies have shown the expression of PG receptors in different cell types of the uterus, we still do not fully understand their functions in different cell types, how they are regulated and their implications in normal health and diseases. Better understanding of the PG receptor signaling mechanism would offer valuable insight that could be used for diagnosis and therapy.

Keywords: Prostaglandin receptors; uterus; endometrium; myometrium; cervix

***Abbreviations*:** Prostaglandin, PG; Cyclooxygenase, COX; 17β-estradiol, E2; Progesterone, P4

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Introduction

Prostaglandins (PGs) are found ubiquitously and are locally produced in most nucleated cells. They are small hormone-like lipids with autocrine and paracrine functions and they maintain local homeostasis in the body [1]. PGs are synthesized from arachidonic acid by cyclooxygenases and prostanoid synthases (Figure 1). There are four major bioactive PGs produced *in vivo*: prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), prostaglandin D_2 (PGD_2) and

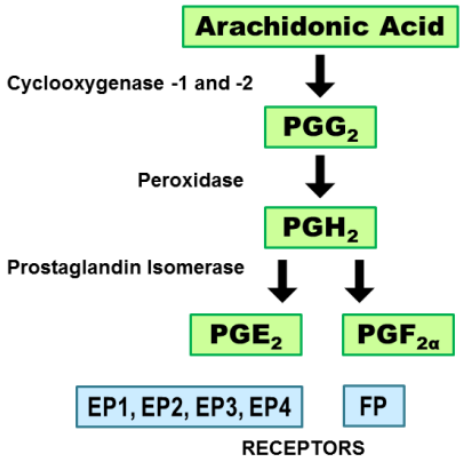

Figure 1. Synthesis of prostaglandins PGE_2 and $PGF_{2\alpha}$ and their respective receptors. Arachidonic acid is processed by the cyclooxygenase (COX) enzymes (COX-1 and COX-2) to form an intermediary precursor, prostaglandin G_2 (PGG_2). It is then converted to prostaglandin H_2 (PGH_2) by the peroxidase enzyme. PGE_2 and $PGF_{2\alpha}$ are derived from PGH_2 by the action of their specific isomerases. PGE_2 binds to its receptors EP1, EP2, EP3 and EP4 whereas $PGF_{2\alpha}$ binds to the FP receptor.

prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) [1]. They exert their effects by binding to specific G protein-coupled receptors thereby activating intracellular signaling and gene transcription [2]. The prostanoid receptor subfamily consists of eight members: E prostanoid receptor (EP) 1, EP2, EP3 and EP4 subtypes of the PGE receptor; PGF receptor (FP); PGD receptor (DP1); PGI receptor (IP); and thromboxane receptor (TP) [1]. These receptors have distinct biochemical properties, localization and differential affinity to ligands [3]. The signaling mechanisms of PGs are different when transduced via different receptors. EP1 signaling is coupled to Ca^{2+} mobilization [4]. EP2 and EP4 trigger the stimulation of adenylyl cyclase, whereas activation of EP3 inhibits adenylyl cyclase [5]. The FP receptor triggers stimulation of phospholipase C-inositol triphosphate as well as Ca^{2+} mobilization [5,6]. In this review we will focus on the roles of EP1-4 (also denoted PTGER1-4) and FP (PTGFR) in the uterus.

PGs are key molecules in reproductive biology, regulating various reproductive processes including ovulation, endometrial regulation, menstruation and parturition. The uterus is fundamental for the survival of the species of viviparous animals. Implantation of fertilized eggs in the endometrium is a critical event in these species. The endometrium undergoes well defined cycles, anticipating the embryo, in preparation for implantation. These cycles of proliferation, differentiation, degradation and menstruation are finely tuned by the endocrine and paracrine environment involving PGs [7-9]. Recent studies show that PGs are essential during implantation and PG receptors facilitate embryo adhesion [10]. PGE_2 and $PGF_{2\alpha}$ acts in a temporal and cell-specific manner via its different receptors around the time of implantation and are important for blastocyst spacing, implantation and decidualization in mouse endometrium [6]. During parturition the myometrium is active in expelling the fetus and PGs are important for proper labor and ripening of the cervix to occur [8,11,12].

The important role of PGs in uterine function was initially discovered over half a century ago [13-16]. Numerous studies have been performed ever since to show their various functions and signaling mechanisms in different uterine cell types. As early as 1976, Schillinger and Prior published evidence for the presence of specific binding sites for PGE_2 and $PGF_{2\alpha}$ by doing saturation analyses in human uterine tissues [17]. Several studies were performed in the 1980s to show binding sites for PGE_2 and $PGF_{2\alpha}$ in different uterine cell types and how they changed throughout the menstrual cycle [18,19]. After the cloning and characterizations of PG receptors in the 1990s plenty of work has been done on their structure, function and gene regulations [4,20,21]. Although PGs are widely used to induce cervical ripening, for labor induction and for termination of pregnancy [22,23], the cell specific expressions of different PG receptors in the uterus was not known until recently. The objective of this review is to compile data on the expression and roles of EP1-4 and FP receptors in endometrium, myometrium and cervix.

Prostaglandin receptors in endometrium

The endometrium consists of luminal and glandular epithelium, stromal tissue and blood vessels. It undergoes constant remodeling throughout the reproductive cycle in the non-pregnant uterus preparing itself for embryo implantation. Upon implantation, the endometrium proliferates and supports the fetus, but in the absence of implantation endometrial lining is shed and a new cycle begins. This cycle is regulated by the sex steroid hormones estradiol (E2) and progesterone (P4) and these hormones modulate the expression of PG receptors like EPs and FP. The receptors, when activated by their specific ligands, are essential for many vital functions in the endometrium.

EPs and FP are expressed in a cell-specific and temporal fashion during the peri-implantation period and decidualization in mice [24-27]. Progesterone has been shown to upregulate the expression of EP2 and E2 further

enhances EP2 expression; while E2 alone suppresses the expression [26]. EP2 mRNA expression is increased during pregnancy in the rat and the level decreases during labor and after delivery, suggesting the likely contribution of P4 in the regulation of EP2. Furthermore, P4 has been found to upregulate EP2 mRNA in the uterus of the ovariectomized rat [28]. Recently we showed the expression of EP1-4 and FP in different cell types of the rat uterus and how the expression differed between various types of cells and treatments [29]. The mRNA expression of EPs and FP was decreased by E2 treatment and the estrogen receptor (ER)α selective agonist PPT, but by the ERβ selective agonist DPN only expression of EP2 and EP4 was downregulated. However, E2 treatment increased the protein levels of EP2 and EP3. When treated with a combination of E2 and P4, expression of EP1 and EP3 was upregulated [29]. Thus, expression EP1, EP3 and FP is regulated by E2 mainly via ERα, whereas EP2 and EP4 are also modulated by the ERβ specific ligand.

Immunohistochemical analyses showed that PG receptors are regulated by ovarian steroids in a cell type specific way. E2 upregulated EP2, but EP1 and EP3 were upregulated when co-treated with E2 and P4. These observations indicate that E2 and P4 regulate EPs and FP in a receptor and tissue specific manner [29].

PGE_2 facilitates the uterine preparation for implantation in the endometrium and this process seem to be mediated by EP3 and EP4 subtypes in epithelial cell differentiation, stromal cell proliferation, uterine edema, luminal closure and increased vascular permeability at blastocyst attachment sites [6]. An investigation on human endometrial tissue displayed the expression of PG receptors to vary during the menstrual cycle in a stage specific fashion with FP increasing during the proliferative phase, EP1 dominating in the early-secretory phase and EP2, EP3 and EP4 dominating in the mid-secretory phase [30]. These observations suggest that E2 and P4 may regulate the expression of endometrial EPs and FP, and that these receptors have specific functions in the respective reproductive phase. EP1 transcripts were found in human endometrium using a microarray technique in early and mid-secretary phase, with higher expression in the mid-secretary phase [31]. Further, immunohistochemical analyses showed a strong signal for EP1 in the luminal and glandular epithelium [31]. These data suggests that the EP1 receptor could be important at the time of implantation. Another study showed that peak expression of EP1 is found during the early secretory phase and that the EP1 protein is present in luminal and glandular epithelium [30]. Further, EP1 is localized to the nuclear region of glandular epithelium during proliferative, early secretory and menstrual phases but it is localized in the apical plasma membrane during mid- and late secretory phases [30]. This suggests the possibility that EP1 may have different functions due to its spatial (nuclear vs. cell membrane) and temporal (proliferative vs. secretory) expression [30]. In human endometrium expression of EP1, EP2 and EP3 peaked in the mid-secretory phase concurrent with increased stromal edema, endometrial blood flow and blood vessel permeability [30]. EP4 has been shown to stimulate the proliferation of glandular epithelial cells during the proliferative phase of the menstrual cycle in an ERK1/2- dependent fashion [32]. Studies in sheep showed that early pregnancy, as well as interferon Tau, induces EP2 and EP4 expression in the endometrium. This suggests that EP2 and EP4 are additively mediating PGE_2 signaling in ovine endometrium [33]. These results also indicate a role for EP2 and EP4 in the normal endometrium and in establishing pregnancy. EP3 is involved in the stromal cell proliferation by activating fibroblast growth factor-9 [34]. In human endometrium FP receptors are expressed predominantly in glandular epithelium, stromal and perivascular cells, showing increased expression in the proliferative stage of the menstrual cycle [35]. FP is the dominant subtype during the proliferative phase in the endometrium [30]. It was reported that the epithelial proliferation induced by $PGF_{2\alpha}$ is mediated by the phospholipase C signaling pathway [35]. Ligand activated FP receptors induce changes in epithelial cell morphology and migration, cell proliferation and angiogenesis [36-38]. We also studied the hormonal effects on cyclooxygenase (COX) proteins in the macaque uterus [39]. COX-1 and COX-2 convert arachidonic acid to PGH_2, a precursor for prostanoid synthesis. Constitutively expressed COX-1 and inducible COX-2 regulate the synthesis of PGs [40]. We found that COX-1 immunostaining decreases after treatment with tamoxifen (estrogen agonist in the uterus) or conjugated equine estrogens (CEE) in the endometrial stroma. COX-2 immunostaining in the endometrial stroma is upregulated by combined CEE and P4 treatment, as compared to untreated ovariectomized animals [39]. In glandular epithelium the combined treatment with E2 and P4 increases COX-2 immunostaining as compared to E2 alone or no treatment. Thus, our results indicate that, in the uterus of ovariectomized macaques, COX-1 and COX-2 are differently distributed, hormonally regulated, and COX-1 immunostaining is more prominent than COX-2. Taken together, PGs and their receptors EP1-4 and FP are essential for the normal function of the endometrium and PGs, their receptors as well as their cyclooxygenases are

regulated by the sex steroid hormones E2 and P4.

Prostaglandins, COX enzymes, PG receptors and downstream signaling pathways are involved in angiogenesis, cell adhesion, morphology, motility, invasion, vascular permeability and metastasis. Abnormal distribution, function and downstream signaling of PG receptors lead to several pathological conditions in the female reproductive tract including dysmenorrhea, menorrhagia, endometriosis and cancer. The possible role of PG receptors in disorders of the endometrium could be of importance for development of therapeutic interventions in the future [41].

Smith *et al*. found a significant increase of endometrial COX-1 and COX-2 mRNAs in women with heavy menstrual bleedings [42]. Furthermore, in the endometrium of these women, PGE_2 stimulation caused an increased production of cyclic AMP when compared to women with normal bleeding [42]. These results imply that EPs are involved in heavy menstrual bleedings and their signaling pathways could be exploited potential therapeutic targets in the treatment of heavy menstruations.

The COX pathway is known to be an important factor in tumor development in humans, enhancing both synthesis and signaling of PGE_2. Studies have reported that endometrial carcinomas show higher PGE_2 synthesis and secretion, as well as increased expression and signaling of EP receptors [43-45]. Further, in endometrial adenocarcinomas a significant upregulation was found in the synthesis and signaling of the FP receptor suggesting a possible involvement in enhanced proliferation of epithelial cells [35]. Expression of COX-2 and biosynthesis of PGE_2 are higher in endometrial adenocarcinomas, but the mechanism whereby they regulate endometrial tumor growth is not clear. Catalano *et al*. compared EP receptor expression in endometrial adenocarcinomas with normal endometrium. They found increased expression of EP4 and a decrease of EP1 and EP3 in the carcinomas as compared to normal endometrium [46]. In nude mice grafted with Ishikawa cells and stably transfected with EP4, tumor growth was enhanced along with increased expression of COX-2, when compared to wild type xenografts [46]. The results from this study clearly suggest a role of EP4 in tumor development of the endometrium.

Several studies have shown a role of PGs in endometriosis [47-51]. The significance of PGE_2 in endometriosis is well documented and reviewed by Sacco *et al* and Wu *et al* [52,53]. These studies clearly show that EP receptors are involved in endometriosis. Recent studies show that inhibition of EP2 and EP4 signaling decreases the migration of human endometriotic epithelial and stromal cells via multiple mechanisms involving matrix metalloproteinases (MMPs) [54]. Further, they also show that inhibition of EP2 and EP4 decreases integrin signaling and activates intrinsic apoptotic mechanisms [55,56]. Although the exact mechanisms are not known, microarray studies have shown that EP3 down regulation also plays a role in endometriosis [57,58].

Prostaglandin receptors in myometrium

PGs are important for the initiation and maintenance of labor. Elevated uterine PG levels or increased sensitivity to PGs in the myometrium lead to contractions and labor [59]. PG receptors EP1-4 and FP have been localized in uterine smooth muscle cells and their role in normal labor is well documented [6,60-63]. The response to PGs in the myometrium may be defined by the type and amount of the receptor expressed [64]. Contractility of myometrium is mediated by EP1, EP3 and FP, whereas EP2 and EP4 mediate relaxation [65]. These receptors mediate contractility and relaxation of smooth muscle cells via different signaling pathways [2]. Pathological expression and signaling have been shown to result in preterm labor [59].

PG receptors play various roles in myometrium around the time of embryo implantation in mice. Yang *et al*. showed that PGE_2 and $PGF_{2\alpha}$ receptor genes are expressed in a temporal and cell-specific manner in the mouse uterus during the peri-implantation period [6]. Expression of EP3 and FP is primarily localized to the myometrial circular muscles on days 3 to 5 of pregnancy indicating the circular muscle layer to be the major target for PG-mediated uterine contractions essential for embryo transport, spacing, and implantation [6].

Grigsby *et al*. investigated if the change from quiescence to contractility in the uterus could depend on different expression of PG receptors within the myometrium. They examined paired upper and lower segment myometrium for the localization and expression of EP1-4 and FP throughout human pregnancy [61]. They found that all receptor subtypes are present in all myometrial layers, but an alteration in intracellular localization at term labor, when EP1 and EP4 are predominantly located in the nucleus. No changes were observed in the expression of PG receptor subtypes in connection to gestational age, labor, or between the upper and lower segments. The authors conclude that myometrial activation via the PG receptors might be defined by the balance between the PG receptor subtypes in addition to other proteins associated to contraction [61].

Further, differential distribution of PG receptor subtypes in different regions of the uterus appears to facilitate relaxation of the lower reproductive tract while simultaneously contracting fundal myometrium [66]. The mRNA expression of EPs and FP did not show any gestational age related changes. However, regional localization of the receptors varied with higher mRNA expression of myometrial EP1 and EP3 in fundus when compared to the lower segment, whereas expression of EP2 is lower in fundus [60]. Labor is associated with a decrease in regional variation of EP2 and an overall lower EP2 expression, but not with the expression of EP1 and EP3. Thus, regional and labor-related variation of PG receptor expression in the myometrium may be crucial for parturition in primates [60].

Abnormal PG signaling has been implicated in pre-term labor [59,67]. The FP receptor is associated with labor at term and it is known to cause myometrial contractions in contrast to EP2 which maintains uterine quiescence [68]. The balance between the two receptor isoforms might be responsible for myometrial contractility [68]. A recent study showed that $PGF_{2\alpha}$ regulates uterine activation via various proteins like connexin-43, EP2, oxytocin receptor and FP expression in myometrial cells from both upper and lower segments leading to uterine activation for the onset of labor [69].

Knowledge on the role of PGs and their receptors in labor gave ample clues to use them as a target to treat pre-term labor. Olson and Ammann presented results on the role of PGs and their receptor inhibitors to treat preterm labor [59]. They showed that COX-2, a regulator of PG synthesis, could be a potential therapeutic target for the prevention of preterm labor. However, non-steroidal anti-inflammatory drugs which inhibit COX enzymes and suppress preterm labor in animals cannot be used due to its adverse effects on the development of the fetus. Using a novel FP antagonist, THG-113.31, the authors showed that, in mice and sheep, preterm birth can be delayed without any maternal or fetal side effects, offering hope for counteracting preterm birth [59]. Another FP antagonist, AS604872, was shown to reduce spontaneous uterine contractions in a dose-dependent fashion in late-term pregnant rats [70]. Further, in pregnant mice the antagonist delayed preterm birth caused by the administration of RU486 [70]. Thus, a selective FP antagonist might one day be used for treating preterm labor in a subset of patients with uterine hyperactivity [70].

Prostaglandin receptors in cervix

Cervix is the uterine neck and acts as a sphincter of the uterus. It undergoes changes throughout the reproductive cycle and pregnancy. During pregnancy the cervix functions as a protective barrier from attacking pathogens and as a physical barrier to keep the fetus in the uterus until parturition [71]. Towards the end of pregnancy the cervix becomes softer and more pliable to allow passage of the fetus, by a process known as cervical ripening. Cervical remodeling occurs in various stages including softening, ripening, dilation and repair with distinct regulations for each process [71]. Disorders of cervical remodeling cause serious pregnancy complications. Pathological regulation of cervical remodeling leads to preterm or post-term labor. Cervical incompetence or an early softening and dilatation result in preterm birth, while inadequate ripening of the cervix at term may lead to dysfunctional labor [72].

PGs play important roles in cervical ripening and labor induction [72-77]. Their involvement is firmly established at the later phases of cervical remodeling, when there is an inflammatory-like reaction in the ripening cervix [72]. PGE_2 increases the concentration of glycosaminoglycan and the activity of elastin contributing to cervical ripening [78]. Further, it has also been suggested that PGE_2 regulates the synthesis of glycosaminoglycan [79], which has been shown to induce cervical ripening by remodeling the extracellular matrix by dispersing and separating the collagen bundles [80]. Our earlier studies showed that MMPs are vital for cervical ripening [81,82]. The presence of PG receptors in cervix has been reported in humans, baboons, rodents and goats [12,83-87]. In the estrus stage of ewes, cervical relaxation is regulated by alterations in PG synthesis and changes in the extracellular matrix of the cervix [79,88,89]. Wu *et al*. showed by *in situ* hybridization and northern blot that uterine segments from pregnant baboons exhibit a gradient in COX-2 mRNA expression. The highest levels were found in lower cervix and the expression decreases in the mid- and upper part of the cervix and lower uterine segment, with the lowest level seen in uterine fundus [90,91]. Another study showed that E2 regulates cervical levels of COX-2 and EP4 mRNAs and may via the synthesis of PGE_2 regulate cervical relaxation as well as activation of EP2 and EP4 receptors [92]. This study is in agreement with our results from the rat uterus where EP2 was found to be regulated by E2 [29]. Increased local production of PGs may be important for pregnancy-associated elongation of the lower uterine segment, cervical softening and effacement in primate labor [90]. These studies show that changes in the lower uterine segment and cervix before the onset of labor is regulated in a synchronous fashion with changes in the myometrium. In pregnant baboons, the expression of EP1 increased with

advancing gestational age prior to labor [12]. However, EP2 and EP4 expressions are down regulated 4- and 2- folds respectively, in animals in labor when compared to those not in labor, indicating that variations in relative expression of PG receptor types could be of importance in cervical dilatation during primate parturition [12].

PGs are widely used to induce cervical ripening for labor induction and for terminations of pregnancies [22,23]. Since the late 1970s, vaginal and intra-cervical application PGs and its synthetic analogs have been shown to induce cervical ripening and onset of labor [93,94].

Since the PGs have a ripening effect on the cervix, we studied the expression and localization of PG receptors EP1-4 and FP. Recently we showed the presence of PG receptors in the cervix of non-pregnant (NP), term pregnant (TP) and post-partum (PP) women and their variable expression in NP, TP and PP states and different cell types [87]. We hypothesized that expression of cervical PG receptors may be different in TP, PP and NP women [87]. We showed that the levels of EP1-4 and FP varied between the NP, TP and PP states and between different cell types [87]. Our data showed that EP2 and EP4 mRNA levels are at their lowest in the TP group. Thus, expressions of both the smooth muscle relaxing EPs are at their lowest levels in pregnancy, before the final ripening has started. The relaxatory action by smooth muscle cells, together with the timed action of tissue remodeling enzymes, could lead to cervical ripening. The absence of regulation of the contraction inducing PG receptors mRNA and protein levels in most of the cell types, suggest that they may not play any active role in the cervical ripening process. Similar observations and conclusions have been made in rats [83].

Although PGE_2 is widely used to induce cervical ripening, in a subset of women with post-term pregnancies PGE_2 fails to induce cervical ripening and labor, leading to delivery by caesarean section [95]. In order to identify the reasons for such different responses, we undertook a series of studies to identify the factors that are differentially expressed between the two groups. We demonstrated that in TP women, PGE_2 induced cervical ripening showed higher collagen concentration in the cervix when compared to women undergoing spontaneous cervical ripening, showing that the PG induced ripening process is not identical to the spontaneous process [96]. Further, glutaredoxin, a member of the thioredoxin superfamily, was 3-fold more expressed in cervix from PGE_2-treated women when compared with women undergoing spontaneous cervical ripening and delivery [97]. These results indicate that glutaredoxin could have a role in the regulation of cervical ripening in humans and that it is regulated by PG treatment [97]. In another study we found that a post-term group responding to PGE2 priming displays lower total progesterone receptor (PR) and androgen receptor (AR) levels compared with non-responders of PGE_2 treatment, and decreased PR-B and AR protein levels when compared with controls, i.e. women who underwent spontaneous cervical ripening. Also the PR mRNA level is decreased in responders when compared with non-responders [98]. When examining COX-1 and COX-2 proteins levels by immunohistochemical analyses in the cervix of post term women, responding or not responding to PG priming for labor induction, we found no differences between the groups [98]. This could be due to oxytocin treatment, since oxytocin can initiate COX-2 gene transcription in human myometrial cells *in vitro* [99]. In addition, mechanical stretch also induces COX-2 activity. We also found that the influx of leukocytes is strongest in the responders to PG treatment, followed by the controls with spontaneous parturition at term and the influx was significantly lower in the non-responders [95]. We concluded that in responders, PGE_2 priming is followed by a functional progesterone and androgen withdrawal at the receptor level and an influx of leukocytes. Impaired leukocyte influx in post term women not responding to PGE2 treatment could be one explanation of the failed cervical ripening.

In order to increase knowledge of the function of PG receptors in cervical ripening we recently investigated the expression and localization of PG receptors in post-term human cervix, after failed or successful induction of labor with PGE_2. We found that expression of EP4 mRNA was downregulated simultaneously with an upregulation of EP3 mRNA levels in the cervix from non-responders when compared with responders. In stroma, EP4 immunoreactivity was higher in non-responders when compared with responders [100]. We concluded that lack of cervical ripening, after local treatment of PGs for labor induction, could be due to the higher expression of EP3 simultaneously with decreased EP4 expression.

Conclusions

PG receptors play many vital roles in the endometrium, myometrium and cervix. Their differential roles in the reproductive cycle and pregnancy are still not clearly understood. Only a handful of studies have been performed showing their spatio-temporal expression in the human uterus. We still do not know their functions in

different cell types, how they are regulated and their full implications in normal health and disease. Although plenty of studies have been done on PG synthesis, secretion and the role of various enzymes in their conversions, we have not yet fully understood the role of PG receptors, their regulation and molecular mechanisms.

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Conflict of interest

The authors declare that there is no conflict of interest.

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